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10/044,219	11/19/2001	Brian J. Stockman	6283NCP2	9179

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MUETING, RAASCH & GEBHARDT, P.A.
P.O. BOX 581415
MINNEAPOLIS, MN 55458

EXAMINER
BAKER, MAURIE GARCIA

ART UNIT	PAPER NUMBER
1639	11

DATE MAILED: 05/19/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

File

Office Action Summary	Application No. 10/044,219	Applicant(s) Stockman et al
	Examiner Maurie G. Baker, Ph.D.	Art Unit 1639

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *THREE* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Feb 28, 2003*.

2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-55* is/are pending in the application.

4a) Of the above, claim(s) *1-45* is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *46-55* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☒ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). *7 & 9*
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

1. The Response filed February 28, 2003 (Paper No. 10) is acknowledged. No claims were cancelled or amended and claims 47-55 were added. Therefore, claims 1-55 are pending.

Election/Restriction

2. Applicant's election of Group VI (claim 46) is acknowledged. Newly added claims 47-55 read on the elected group.

3. Applicants argue that "the inventions as claimed can be readily evaluated in one search without placing undue burden on the Examiner". The examiner respectfully disagrees. The Restriction Requirement sets forth the rationale for why the inventions are distinct. Moreover, the groups that describe the different inventions each have different issues regarding patentability and enablement, and represent patentably distinct subject matter, which merits separate and burdensome searches. Art anticipating or rendering obvious each of the above-identified groups respectively would not necessarily anticipate or render obvious another group, because they are drawn to different inventions that have different distinguishing features and/or characteristics. Each group could support a separate patent.

4. Thus, as stated in the Restriction Requirement, the different inventions would require different searches, and there is no expectation that the searches would be coextensive. Therefore, this does create an undue search burden, and restriction for examination purposes as

indicated is proper and is made FINAL. Claims 1-45 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to non-elected inventions.

5. Therefore, claims 46-55 are under examination.

Priority

6. Applicant's claim for domestic priority under 35 U.S.C. 119(e) is acknowledged. However, applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 119(e) as follows:

> The instant application is a continuation-in-part of application 09/677,107, which claims priority to provisional applications 60/516,818, 60/161,682 and 60/192,685. However, all of the provisional applications upon which priority is claimed fail to provide adequate support under 35 U.S.C. 112 for the *full scope* of the claims of this application since they do not contain a reference to WaterLOGSY NMR. Note that a broad generic disclosure is **not** sufficient support for a specific entity within the class. Thus, claims 46-55 are only awarded the filing date of application 09/677,107, which is 9/29/00.

Specification

7. The incorporation of essential material in the specification by reference to a foreign application or patent, or to a publication is improper. See instant specification, page 14, lines 3-4 where the Dalvit et al, J. Biomol. NMR, 18, 65-68 (2000) reference is mentioned. Applicant is required to amend the disclosure to include the material incorporated by reference. The

amendment must be accompanied by an affidavit or declaration executed by the applicant, or a practitioner representing the applicant, stating that the amendatory material consists of the same material incorporated by reference in the referencing application. See *In re Hawkins*, 486 F.2d 569, 179 USPQ 157 (CCPA 1973); *In re Hawkins*, 486 F.2d 579, 179 USPQ 163 (CCPA 1973); and *In re Hawkins*, 486 F.2d 577, 179 USPQ 167 (CCPA 1973). It is noted while the instant application does describe WaterLOGSY NMR to some extent, this is not deemed sufficient without the disclosure of the Dalvit et al, J. Biomol. NMR, 18, 65-68 (2000) reference.

8. The disclosure is objected to because of the following informalities: The disclosure mentions at several places that one of the advantages of the WaterLOGSY NMR method is that low levels of target molecule can be used. Preferred ratios of target to ligand are mentioned, see, e.g. page 5, lines 8-10: "ratios of **ligand** to **target** of about 100:1 to about 10:1" (emphasis added). However, page 14, lines 10-11 states "ratios of **target** molecule to **compounds in each sample reservoir** [i.e. **ligands**] of about 100:1 to about 10:1" (emphasis added). This is confusing and it appears that the recitation on page 14 is in error. This is especially true when taken with the recitation in instant claim 46 of concentration of target molecule = no greater than about 5μM and concentration of each compound in each sample = 125 μM. Appropriate correction to the specification is required. This also affects claim 53, see paragraph 10 below.

Claim Objections

9. Claims 47 and 55 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to

cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form.

Claim 47 recites that the "concentration of the target molecule is no greater than about 10 μM". However, claim 47 depends from claim 46, which recites that the concentration of target molecule = no greater than **about 5μM**.

Claim 55 recites that the "target molecule is a protein". As claim 46, on which claim 55 depends, is drawn to a "method for identifying a protein function", this claim appears to be redundant as the target in question should always be a protein. Also see rejection under 35 U.S.C. 112, second paragraph below.

Claim Rejections - 35 USC § 112

10. Claims 46 and 53 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

The specification as originally filed does not provide support for the invention as now claimed. Claim 53 is newly added in applicant's preliminary amendment filed February 28, 2003. However, this claim recites "wherein the ratio of target molecule to each test molecule in each sample reservoir is about 100:1 to about 10:1" which is not properly disclosed in the specification. While it is true that the specification does recite this particular limitation (see paragraph 8 above and page 14 of the instant specification), it is believed that this is an error and that the ratio should be 100:1 to about 10:1 for

ligand to *target*. This is especially true when taken with the recitation in instant claim 46 (on which claim 53 depends) of concentration of target molecule = no greater than about 5μM and concentration of each compound in each sample (i.e. ligand) = 125 μM.

11. Claim 54 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue". These factors include, but are not limited to:

(1) the breadth of the claims;
(2) the nature of the invention;
(3) the state of the prior art;
(4) the level of one of ordinary skill;
(5) the level of predictability in the art;
(6) the amount of direction provided by the inventor;
(7) the existence of working examples; and
(8) the quantity of experimentation needed to make or use the invention based on the content of the disclosure.

See *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

(1-2) The breadth of the claims and the nature of the invention: The claims are very broadly drawn to a "method of identifying a protein function" using a particular NMR technique (WaterLOGSY). However, claim 54 recites that the "dissociation constant of the test compound that binds to the target molecule is at least about 100μM".

(3 and 5) The state of the prior art and the level of predictability in the art: WaterLOGSY NMR was known in the art at the time of filing (see Dalvit et al, cited below); however, the specification gives no guidance to permit one of skill in the art to devise steps for

determining whether *any* test compound has a dissociation constant of "least about 100μM" with *any* (protein) target. The structures of possible test compounds and sequences of protein targets are sufficiently diverse and one of ordinary skill would not be able to predict their structures. One of ordinary skill could not guess, *a priori*, how to carry out the claimed method where the "dissociation constant of a compound that binds to the target molecule is at least about 100μM" in the absence of any guidance as to the chemical structures of these entities or the steps of the method without undue experimentation. Applicant's claim represents only an invitation to experiment.

(4) The level of one of ordinary skill: The level of skill would be high, most likely at the Ph.D. level. However, such persons of ordinary skill in this art, *given its unpredictability*, would have to engage in undue (non-routine) experimentation to carry out the invention as claimed.

(6-7) The amount of direction provided by the inventor and the existence of working examples: Applicants have provided very limited examples of the claimed method. It appears that the claims omit matter that is essential to the invention (i.e. information on how to determine whether a particular test compound would have a dissociation constant of "least about 100μM" with a particular target). Claim 54 discloses no information on the structures of the compound or target or how the dissociation constant is to be determined. See *In re Mayhew*, 527 F.2d 1229, 188 USPQ 356 (CCPA 1976) regarding omission of essential matter and see also MPEP § 2164.08(c).

(8) The quantity of experimentation needed to make or use the invention based on the content of the disclosure: Therefore, the instant specification does not provide to one

skilled in the art a reasonable amount of guidance with respect to the direction in which the experimentation should proceed in carrying out the claimed invention. Note that there must be sufficient disclosure, either through illustrative examples or terminology, to teach those of ordinary skill how to make and use the invention as broadly as it is claimed. *In re Vaeck*, 947 F.2d 488, 496 & n.23, 20 USPQ2d 1438, 1445 & n.23 (Fed. Cir. 1991). Thus, it is deemed that further research of an unpredictable nature would be necessary to carry out the invention as claimed.

Claim Rejections - 35 USC § 112

12. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

13. Claims 46-55 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A. Claim 46 is incomplete as the object of the method is not obtained. This renders the claim indefinite. The claim is drawn to a "method for identifying a protein function"; however, there are absolutely no steps drawn to accomplishing this goal. Instead, the claim merely states in the last step "determining the function of the target molecule". See also section B below.

B. Moreover, claim 46 is confusing and indefinite because it refers in the method steps to a "target molecule" (in general) but the claim is drawn to a "method for identifying

a protein function". A claim which fails to interrelate essential elements of the invention may be rejected under 35 U.S.C. 112, second paragraph, for failure to point out and distinctly claim the invention. See *In re Venezia*, 530 F.2d 956, 189 USPQ 149 (CCPA 1976); *In re Collier*, 397 F.2d 1003, 158 USPQ 266 (CCPA 1968). Claims 47, 48, 53 and 54 are indefinite for the same reason.

C. Claim 47 is confusing in the recitation of the "concentration of the target molecule is no greater than about 10 μM". Claim 47 depends from claim 46, which recites that the concentration of target molecule = no greater than **about 5μM**. See also paragraph 9 above.

D. Claim 53 recites "wherein the ratio of target molecule to each test molecule in each sample reservoir is about 100:1 to about 10:1". This is very confusing when taken with the recitation in instant claim 46 (on which claim 53 depends) of concentration of target molecule = no greater than about 5μM and concentration of each compound in each sample (i.e. ligand) = 125 μM. The recitation in claim 53 is believed to be an error and that the ratio should be 100:1 to about 10:1 for *ligand* (i.e. test molecule in each sample reservoir) to *target*. The claim is interpreted in this manner for the purposes of this action. See also paragraphs 8 & 10 above.

E. Claim 54 recites that the "dissociation constant of the test compound that binds to the target molecule is at least about 100μM". However, it is completely unclear as to applicants intent as there is not a structure present for either the target or the compound and no method steps for determining the dissociation constant. Therefore, the claim is incomplete and unclear.

F. Claim 55 is confusing and indefinite because it recites that the "target molecule is a protein". As claim 46, on which claim 55 depends, is drawn to a "method for identifying a protein function", this claim appears to be redundant as the target in question should always be a protein. See also sections A & B above and paragraph 9.

Claim Rejections - 35 USC § 103

14. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

15. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

16. Claims 46-55 are rejected under 35 U.S.C. 103(a) as being unpatentable over Dalvit et al, (J. Biomol. NMR, 2000; on PTO-1449) in view of Keifer et al (J. Combi. Chem. 2000; on PTO-1449).

It is noted that the Dalvit reference was published in September 2000, but at the bottom of page 65 it is stated that the work in the article was presented at a conference on February 19, 2000. Also, applicants cite this article on page 14, lines 3-4 of the instant specification.

Dalvit et al teach a "powerful screening by NMR methodology (WaterLOGSY)" (see Abstract). In fact, Dalvit et al coin the term WaterLOGSY on page 67, 2nd column. A mixture of "10 low molecular weight compounds (concentration 100μM)" in the presence of 10μM of protein is tested for compound binding (page 67, 2nd column and Figure 1). This reads on the limitations of claims 47, 49, 50, 52, 53 and 55. The WaterLOGSY NMR spectra are compared with a reference spectrum (see Figure 2 and accompanying text, especially page 68, 1st column, top). Both 1D and 2D WaterLOGSY spectra are taken (pages 67-68), reading on instant claim 51. The compounds of the mixture of Dalvit have NMR signals "consisting mostly of sharp singlets", reading on claim 52. The solubility (instant claim 50) and dissociation constant (instant claim 54) are intrinsic features of a compound and thus are deemed to be taught by the compounds tested in the method of Dalvit et al, absent evidence to the contrary. Also, the reference teaches "the sensitivity of the method to protein concentrations as low as a few hundred nM" (page 68, 1st column), reading on the limitations of claims 48.

The reference lacks the teaching of a "plurality of mixtures of test compounds" and using a flow-injection probe.

However, the use of such apparatus and methodology was well established in the art of high-throughput testing/combinatorial chemistry at the time of filing, see for

example, Keifer et al. See the entire teachings of the reference, specifically Abstract and pages 151 & 153 for teachings of the use of flow probes and 96-well plates in a flow NMR technique for the analysis of combinatorial chemistry libraries. The techniques of Keifer et al are specifically for testing libraries, and mixture analysis is also taught (see page 167). This would read on the "plurality of mixtures of test compounds".

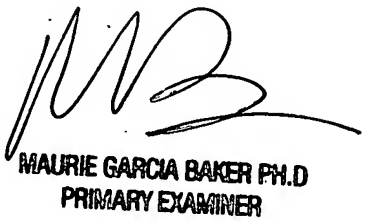
Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to carry out the method of Dalvit et al using a "plurality of mixtures of test compounds" and a flow-injection probe as these are standard in the art as evidenced by Keifer et al. One of ordinary skill would have been motivated to do so due in order to have the advantageous sample handling capacity of Keifer et al and to more easily automate the screening of libraries (see pages 151-152 of Keifer et al for the advantages of their technique).

Status of Claims/Conclusion

17. No claims are allowed.

18. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maurie Garcia Baker, Ph.D. whose telephone number is (703) 308-0065. The examiner is on an increased flextime schedule but can normally be reached on Monday-Thursday and alternate Fridays from 9:30 to 7:00.

19. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew J. Wang, can be reached on (703) 306- 3217. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-4242. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.



Maurie Garcia Baker, Ph.D.
May 16, 2003